Dermatol Ther (Heidelb) (2023) 13:2911–2916
https://doi.org/10.1007/s13555-023-01015-w

LETTER

Letter to the Editor: Response to Fitzgerald T et al. Long-Term Psoriasis Control with Guselkumab, Adalimumab, Secukinumab, or Ixekizumab in the USA

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Received: June 1, 2023 / Accepted: August 15, 2023 / Published online: September 26, 2023

Keywords: Claims data; Clinical interpretation; Methodology; Persistence; Psoriasis

Dear Editor,

We read with great interest the article "Long-term psoriasis control with guselkumab, adalimumab, secukinumab, or ixekizumab in the USA" recently published by Fitzgerald et al. in this journal. The authors compared treatment persistence, reinitiation, and rates of discontinuation in patients with psoriasis initiated on guselkumab, adalimumab, ixekizumab, or secukinumab using administrative claims data. The results demonstrated better persistence and higher remission rates with guselkumab compared to the other biologics studied [1]. With a growing body of literature related to real-world treatment patterns of biologics in psoriasis, we feel there is a particular need for better understanding the methodologies and interpretations of these types of studies to inform clinical context [2].

METHODOLOGY

When considering treatment pattern data, it is important to keep in mind that variability in definitions and methodologies employed among studies can lead to drastically different results, even when using the same data source. This makes it difficult to compare treatment outcomes between studies. When using claims data sets, persistence on a medication is based on prescription refill history. For many reasons (e.g., change of insurance or drug holidays), patients may experience a gap between refills, which is defined as a treatment gap. This gap may be based on a fixed time interval or, alternatively, based on varying gap lengths that correspond to different drug dosing frequencies [3–5]. The published study by Fitzgerald et al. utilized a 2× dosing interval gap definition, which introduces some limitations. For example, in comparing persistence of the available biologics for the treatment of psoriasis and psoriatic arthritis, one biologic is considered non-persistent after 14 days of missed doses, while another biologic is considered persistent even after close to half a year of missed doses. The methodology used by the authors could therefore lead to a bias that unfairly favors IL-23 inhibitors, which are dosed infrequently, and

This comment refers to the article available online at https://doi.org/10.1007/s13555-023-00910-6.

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against other classes of biologics that are dosed more frequently. Therefore, it would be helpful to include sensitivity analyses using treatment gap definitions independent of dosing schedules in future studies measuring treatment persistence. Table 1 gives an illustration of the different treatment gap definitions used for evaluating biologics in psoriasis or psoriatic arthritis. Additionally, the rationale for not including ustekinumab in the current study, because a similar study comparing treatment persistence with ustekinumab and other biologics was recently published by the same group [6], is not scientifically robust. Moreover, inclusion of other IL-23 inhibitors would have helped conclude if study outcomes are related to a class effect specific to IL-23 inhibitors versus guselkumab alone.

Second, days of supply in claims databases could vary and may differ from the recommended dosing duration. Imputation on days of supply for only one of the drugs being compared that differed from the recommended dosing duration could introduce bias in persistence analysis [7].

Third, Fitzgerald et al. did not consider adjustment of baseline heterogeneity between treatment groups for potential bias, which is inherent in observational studies. Assessment of heterogeneity in observational studies should consider methods to control confounding, such as matching and re-weighting, for comparative effectiveness [8].

Furthermore, when assessing treatment patterns using administrative claims databases, one should consider evaluating both adherence, which measures the actual days on treatment without counting the gaps, and persistence to provide a more comprehensive assessment of real-world treatment effectiveness. The medication possession ratio (MPR) and proportion of days covered (PDC) are two common methods to estimate adherence or compliance to treatment, which help determine whether a patient is taking their medication as prescribed, regardless of the dosing schedules or treatment gaps. Fitzgerald and colleagues did not report these measures.

CLINICAL INTERPRETATION

We challenge the authors on their use of the terms "disease control" and "remission." While persistence is accepted as a proxy for effectiveness, it is inappropriate to generalize persistence data as "disease control," since persistence data are influenced by many factors, including effectiveness, but also by safety, tolerability, healthcare systems, and patient access to therapy. Regarding remission, a patient with no claims for psoriasis-related treatment post-discontinuation with $\geq$ 6 months of follow-up was defined as in "remission." Yet, claims for topical therapies were allowed, which is incongruent with the definition of remission. Furthermore, this definition of "remission" does not consider the wide variety of factors that contribute to treatment patterns, including loss of insurance coverage or termination of systemic therapies while a patient is pregnant. Importantly, "disease control" and "remission" are complex to define and are both influenced by multiple factors, all of which would require an evaluation of clinical outcome measures that are not contained within administrative claims databases. For data related to disease control and remission, the best sources will be large registries, such as CorEvitas [9], or prospective observation trials, such as the Psoriasis Study of Health Outcomes [10].

Indeed, administrative claims data are helpful in analyzing adherence and persistence patterns of different therapies. It is important to keep in mind, however, the nuances associated with such analyses and to interpret the results with caution. Finally, we assert there is a need for consistent and standardized definitions, assessments, and analyses across studies, especially for those evaluating biologics used to treat psoriasis, given the differing dosing intervals. Such standardization would improve interpretation of results, which may help healthcare practitioners utilize real-world treatment data to make treatment decisions for patients with psoriasis.

Table 1 Definition of persistence and treatment gaps used in psoriasis studies

Study details	Data source	Comparators	Definition of persistence
Fitzgerald et al 2023 [1]	IBM MarketScan Commercial and Medicare Supplemental Databases	Guselkumab, adalimumab, secukinumab, and ixekizumab	Discontinuation (or end of persistence) defined as gaps in index biologic supply Two definitions of therapy exposure gaps: • Two times (2×) the per-label dosing interval or mode days of supply (> 120 days for guselkumab and > 60 days for adalimumab, secukinumab, and ixekizumab) • One time (1×) the per-label dosing frequency after the induction phase or the mode of days of supply observed in the data (i.e., guselkumab: > 60 days; adalimumab, secukinumab, ixekizumab: > 30 days)
Blauvelt et al 2022 [11]	IBM Watson Health MarketScan Commercial Encounters, Medicare Supplemental, and Monthly Early View Databases	Ixekizumab and guselkumab	A prescription refill within < 60 or < 90 days of the last day of supply Sensitivity Analyses: Assessment of persistence with allowed gap of 45 days
Pilon et al 2022 [6]	Optum's de-identified Clinformatics Data Mart Database	Ustekinumab, secukinumab, adalimumab, and ixekizumab	Discontinuation was defined as a therapy exposure gap in consecutive days of index agent supply, or between the last day of supply and the end of the follow-up period Two definitions of therapy exposure gap based on the frequency of drug administration after the induction phase: • One time the frequency of administration (i.e., ustekinumab, > 90 days; secukinumab, > 30 days; adalimumab, > 15 days; ixekizumab, > 30 days) • More than twice the frequency of administration (i.e., ustekinumab, > 180 days; secukinumab, > 60 days; adalimumab, > 30 days; ixekizumab, > 60 days) A third definition of discontinuation considered was based on the absence of a therapy exposure gap of > 90 days for all biologics and was used for a sensitivity analysis
Pina Vegas et al 2022 [5]	French National Health Insurance Database (Système National des Données de Santé)	Etanercept, infliximab, adalimumab, certolizumab, golimumab, ustekinumab, secukinumab, ixekizumab, and brodalumab	The time from biologic therapy initiation to discontinuation, discontinuation of treatment was defined as a period of > 60 days without filling a prescription for the same treatment after the period covered by the previous prescription
Xu et al 2022 [7]	IBM MarketScan Commercial Claims and Encounters Database	Adalimumab, certolizumab pegol, etanercept, guselkumab, ixekizumab, secukinumab, and ustekinumab	Continuous filling of a prescription for index biologic medication for at least the first 80% of the follow-up evaluation period (3, 6, 9, or 12 months) Persistence with each index biologic medication was assessed based upon the label-recommended maintenance dosing interval (1× gap) Sensitivity Analyses: Allowable treatment gaps of twice the label-recommended maintenance dosing interval (2× gap) and a fixed 90-day period (90-day gap)
Schmitt-Egenolf et al 2021 [12]	Swedish National Patient Register (NPR), the Prescribed Drug Register (PDR) and the Cause-of-Death Register	Adalimumab, infliximab, etanercept, ustekinumab, guselkumab, secukinumab, ixekizumab, and brodalumab	The time in days from the first administration to the end of drug supply following the last administration The allowed gap between administrations (i.e., from the end of supply of the former administration to the administration date of the next) was < 90 days

Table 1 continued

Study details	Data source	Comparators	Definition of persistence
Wu et al 2021 [13]	Optum Clinformatics Data Mart	Adalimumab, apremilast, etanercept, secukinumab, and ustekinumab	Number of elapsed days between the last day of supply of a fill and its subsequent fill date, varied based on each medications' labeled maintenance dosing frequency Sensitivity Analyses: • 2× the maximum allowed gap used in the default analysis • A fixed 90-day gap was used for all study medications
Yiu et al 2020 [14]	British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR)	Adalimumab, ustekinumab, and secukinumab	Discontinuation of therapy defined as any gap in treatment for > 90 days
Murage et al 2019 [2]	IQVIA PharMetrics Plus	Adalimumab, etanercept, infliximab, secukinumab, and ustekinumab	Time to discontinuation of biologics overall, or by individual biologic, with a 90-day permissible gap
Sbidian et al 2019 [15]	French National Health Insurance Database (SNIIRAM)	Etanercept, infliximab, adalimumab, and ustekinumab	The time interval between initiation and discontinuation, where discontinuation of treatment was defined as a period of > 90 days without fulfilment of a prescription for the same treatment after the period covered by the previous prescription
Sruamsiri et al 2018 [16]	Japan Medical Data Center Co., Ltd. (JMDC) Database	Infliximab, adalimumab, secukinumab, and ustekinumab	The time from treatment initiation (index date) until discontinuation of the index biological therapies Discontinuation was defined as a period of 90 consecutive days without the index biological therapy (non-biological therapy refill period – the sum of the treatment interval and medication gap) for adalimumab, infliximab, secukinumab, or 150 days for ustekinumab was found; or the patient switched from the index treatment to other treatment(s) during follow-up A medication gap of 60 days was used for all biological therapies

Medical Writing and Editorial Assistance Medical writing assistance was provided by Gillipsie Minhas, PhD, an employee of Syneos Health, and funded by Eli Lilly and Company.

Author Contributions. Alyssa Garrelts, William Malatestinic and Meghan Feely were involved in the conception of the work. Alyssa Garrelts and Julie Birt were involved in the design of the work. Alyssa Garrelt was involved in drafting of the work. Andrew Blauvelt, Alyssa Garrelts, William Malatestinic, Julie Birt, Baojin Zhu and Meghan Feely were involved in the interpretation of the data for work as well as the critical revision to the work.

Funding. This study and Rapid Service Fee were funded by Eli Lilly and Company (Indianapolis, Indiana, USA).

Declarations

Conflict of interest. Andrew Blauvelt has served as a speaker (received honoraria) for AbbVie, Bristol-Myers Squibb, Eli Lilly and Company, Pfizer, Regeneron, and Sanofi, served as a scientific adviser (received honoraria) for AbbVie, Abcentra, Aclaris, Affibody, Aligos, Almirall, Alumis, Amgen, Anaptysbio, Apogee, Arcutis, Arena, Aslan, Athenex, Bluefin Biomedicine, Boehringer Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, CTI BioPharma, Dermavant, EcoR1, Eli Lilly and Company, Escient, Evelo, Evommune, Forte, Galderma, HighlightII Pharma, Incyte, InnoventBio, Janssen, Landos, Leo, Lipidio, Merck, Nektar, Novartis, Pfizer, Rani, Rapt, Regeneron, Sanofi Genzyme, Spherix Global Insights, Sun Pharma, Takeda, TLL Pharmaceutical, TrialSpark, UCB Pharma, Union, Ventyx, Vibliome, and Xencor, and has acted as a clinical study investigator (institution has received clinical study funds) for AbbVie, Acelyrin, Allakos, Almirall, Alumis, Amgen, Arcutis, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Concert, Dermavant, Eli Lilly and Company, Evelo, Evommune, Galderma, Incyte, Janssen, Leo, Merck, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma, UCB Pharma, and Ventyx. Alyssa Garrelts, William Malatestinic, Julie Birt, Baojin Zhu are current employees and shareholder of Eli Lilly and Company. Meghan Feely is an associate staff member at Mount Sinai Hospital; is a current employee and shareholder of Eli Lilly and Company; has received consulting, travel, or speaker fees from American Academy of Dermatology, Aerolase, Castle Biosciences, CeraVe-L'Oréal, DREAM USA, Galderma Aesthetics, Glow Recipe, La Roche-Posay-L'Oréal, Revian, Sonoma Pharmaceuticals, Sun Pharma, and Suneva Medical.

Ethical Approval. This letter is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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